REVIEW

Exploring the Impact of Iron Deficiency Anaemia on Glycated Haemoglobin A1c Levels in Pregnant and Non-Pregnant Women: A Systematic Review

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Abstract: Haemoglobin A1C (HbA1c) is fundamental in monitoring glycaemic control during pregnancy. However, several conditions could affect this test's accuracy, including iron deficiency anaemia (IDA). Hence, this systematic review delves into the underexplored connection between IDA, iron replacement therapy (IRT), and haemoglobin A1C (HbA1c) during pregnancy. An electronic search of the Cochrane, MEDLINE, and Embase databases was conducted by six authors. From a comprehensive search strategy, 968 records were obtained. After applying the inclusion and exclusion criteria, seven studies were included, comprising 365 women selected for analysis. Six studies indicated a positive correlation between IDA and HbA1c levels, while one found no correlation. The average HbA1c level of the included studies in pregnant women was 5.64%. In comparison, it was found that non-pregnant women had lower HbA1c levels. Among the included studies, the mean HbA1c levels decreased from 5.1% to 4.89% after treating pregnant women with IRT. The review emphasises the complexity of interpreting HbA1c levels in pregnant women with IDA, highlighting the influence of pregnancy-induced physiological changes. In addition, this suggests that HbA1c should not be the sole criterion for diabetes management in pregnant women with IDA. Future research should focus on alternative glycaemic monitoring methods unaffected by IDA.

Keywords: iron deficiency anaemia, iron replacement therapy, pregnancy, gestational diabetes, glycated haemoglobin, HbA1c

Introduction

Haemoglobin is a fundamental component of blood, containing heme, a porphyrin that holds iron. Iron is critical for various functions within the human body (eg binding to oxygen, regulating energy in macrophages, enhancing protein and oxidative capacity in skeletal muscles). The diverse roles of iron underscore its indispensability in human physiology. The iron levels in pancreatic islet beta-cells are closely related to blood glucose levels, and markers of iron metabolism (eg, transferrin, ferritin, hepcidin, and transferrin receptors) influence the development and progression of gestational diabetes mellitus (GDM).[1–3] Consequently, understanding the process of iron metabolism, from ingestion to excretion, sheds light on the impact of iron deficiency anaemia (IDA) on an individual's glycaemic status. To clarify, individuals consuming a balanced diet with both animal- and plant-based iron sources and maintaining optimal digestive and bowel health are better positioned to maintain iron homeostasis. Conversely, those with conditions affecting these processes (eg Celiac disease) may experience low iron levels, leading to IDA, which affects their glycaemic status, particularly haemoglobin glycation A1C level (HbA1c).[4–6]

The World Health Organisation (WHO) reports that among females of reproductive age (15–49 years old), the prevalence of anaemia is 29.9%. This prevalence increases to 36.5% among pregnant females in the same age group.[7]

There are pregnancy-related physiological changes (eg increased iron demand) that deem these women at risk of developing anaemia, of which the most prevalent type is IDA.[8] IDA in pregnancy is linked to negative consequences for both the mother and child (eg higher risks of death for the mother, foetus, and newborn), as well as poor pregnancy outcomes (eg low birth weight, premature birth, and hindered neurocognitive development).[9–13]

IDA typically presents asymptomatically in routine medical checkups. Still, it can also manifest through a range of vague signs and symptoms (eg palmar or conjunctival pallor, koilonychia, pica, collapsing pulse tachycardia, fatigue and dizziness, dyspnoea). These symptoms guide physicians in their diagnostic approach, helping to rule out other potential conditions causing anaemia (eg vitamin B12 deficiency). Undertreatment or, if left untreated, IDA during pregnancy can lead to increased morbidity and complications for both mother (eg increased risk for peripartum infections) and foetus (eg intrauterine growth restriction).[14,15] During pregnancy, anaemia can be diagnosed by a serum ferritin concentration below 30 μg/L combined with haemoglobin concentrations below 11 g/dL in the 1st trimester, below 10.5 g/dL in the 2nd trimester, and below 11 g/dL in the 3rd trimester. This diagnostic criterion indicates the presence of anaemia in pregnant women and is used to assess their iron levels and overall health during pregnancy.[16]

During pregnancy, glycaemic levels should be monitored to limit the risk of adverse outcomes in both the mother and foetus. Studies have shown that HbA1c levels are a strong predictor of maternal and foetal complications during pregnancy.[17] The normal threshold of HbA1c during pregnancy is lower than in the normal population due to pathophysiological changes. Consequently, HbA1c levels >5.4% (36 mmol/mol) in the first trimester, >5.4% (36 mmol/mol) in the second trimester, and >5.7% (39 mmol/mol) in the third trimester would confirm the diagnosis of GDM.[18] Moreover, pregnant women with HbA1c levels exceeding 5.2% had a higher likelihood of experiencing unfavourable pregnancy outcomes (eg a higher risk of preeclampsia).[19] Although studies have discussed a threshold of HbA1c levels and correlated complications, it is crucial to identify the conditions that lead to false increases in HbA1c levels (ie IDA) during pregnancy and establish a relation for clinical considerations.

IDA has been recognized as a significant factor influencing HbA1c levels since Horton and Huisman first explored the condition in 1965.[20] Subsequent studies have yielded conflicting results regarding the impact of IDA on HbA1c levels during pregnancy, with most indicating higher levels in IDA patients,[17,21–25] while others show unchanged levels.[26,27] This study summarizes the current evidence on the difference in HbA1c levels with IDA indicators in pregnant and non-pregnant women. Additionally, this study evaluates the current evidence on the influence of iron replacement therapy (IRT) on HbA1c in these individuals.

Methods
Protocol and Registration
This study adhered to the Cochrane Review methods and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, and it was registered on Prospero under registration number CRD42024496543.[28]

Eligibility Criteria
This review encompasses a wide range of studies focusing on pregnant and non-pregnant women diagnosed with IDA in all ages, races, and nationalities to ensure a diverse and representative sample. We specifically reviewed studies that measured HbA1c levels during pregnancy and studies that included HbA1c measurements in non-pregnant women. The inclusion criteria for pregnant women included 1) a confirmed diagnosis of IDA, 2) not diagnosed with GDM, and 3) women with documented HbA1c levels. The inclusion criteria for non-pregnant women included healthy women with no anaemia, GDM or diabetes mellitus. The study designs included prospective and retrospective studies, randomized and non-randomized trials, cross-sectional studies and case-control studies. The criteria were intended to provide a comprehensive overview of the relationship between IDA and HbA1c levels during pregnancy and to compare them with non-pregnant women. In contrast, studies that did not focus on IDA or did not measure HbA1c for their sample were excluded. Additionally, non-human, duplicate, or poor-quality studies (eg case reports, letters, expert opinions, conference abstracts, and editorials) were excluded.

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Information Sources

A search for relevant literature was done on July 22,2023, utilising major databases such as the Cochrane Central Register of Controlled Trials (OvidSP), MEDLINE (ProQuest, Ann Arbour, MI, USA) and Embase (OvidSP) for the period between January 1956 and July 2023. We used a combination of medical subject headings (MeSH) terms and free-text searches focusing on keywords related to "Iron deficiency anaemia" and "HbA1c." The complete list of the keywords used and the search strategy are provided in Supplementary Table 1. These search terms were selected based on examining the titles and abstracts of relevant studies and subject indexing and utilising the PubMed (PubReMiner) tool to analyse word frequency with no language restrictions applied.

Search Strategy

The search strategy was designed so that each database was searched using individually tailored terms and Boolean operators, such as "AND" or "OR." The primary search keywords were in English to correctly identify studies in the databases used; however, we did not limit our search by language so that a broad range of global studies could be captured (ie any non-English study within our search scope was included and translated for further assessment). In addition to database searches, we conducted manual searches of the reference lists of the included studies and used search engines (eg Google Scholar). This dual approach was intended to ensure that no relevant study was overlooked.

Selection Process

PRISMA flow diagram guided the selection of the included studies, in which the process started with identifying records through database searching and additional sources. We used reference management software (Mendeley) to remove duplicates. The studies' titles were scrutinised for relevance, followed by an abstract and a full-text assessment to determine eligibility. Accordingly, the process required us to split the studies into two groups for an improved evaluation of the studies. The first group was assessed independently using AMA, MAS, and HJA, while the other group was evaluated using OAB, MAA, and AHA. Any disagreement between reviewers during this process was resolved through discussion, ensuring a consensus-based approach to data extraction. Throughout this process, we documented reasons for excluding studies at each stage to maintain the transparency and reproducibility of our review process. Any non-English articles identified were translated to assess their suitability for inclusion. To obtain essential details and necessary data, the authors of six studies were contacted for additional information.

Data Collection Process

Data extraction was carried out by three independent authors using a customised Excel spreadsheet. This included details such as the study's author(s), type, objectives, sample size, inclusion and exclusion criteria, year and country of publication, and setting. The data collection was comprehensive, covering aspects related to IDA (ie ferritin, transferrin, haemoglobin, iron level, mean corpuscular volume [MCV], mean corpuscular haemoglobin [MCH]) and HbA1c (ie levels pre- and post-IRT in pregnant and non-pregnant women, techniques of measurement and relevance in the context of IDA). The utility of these suggested parameters' form was pilot-tested by all team members using relevant records. To confirm its utility, the reviewers worked independently to extract the data from the included records.

Study Risk of Bias Assessment

To assess the quality of the included studies, two authors (MAS and HJA) worked independently using Joanna Briggs Institute critical appraisal checklists suitable for both observational and experimental studies.[29,30] This assessment covered various domains of potential biases (ie selection, performance, detection, attrition, and reporting biases). The aim was to provide a well-rounded evaluation of each study, culminating in an overall risk of bias judgement. Additional information regarding bias evaluation is presented in Supplementary Tables 2 and 3.

Results

Study Selection

Our systematic review began with a pool of 968 records, narrowed down through a selection process, with 127 records removed for duplications. The 830 records excluded during the title screening phase were predominantly due to the irrelevance of the key themes of iron deficiency or HbA1c. The subsequent abstract screening further refined our selection, emphasising specific inclusion criteria related to pregnancy with IDA and the measurement of HbA1c levels in these individuals. This phase led to the exclusion of studies that were not closely aligned with our research focus. Of the 11 full-text articles assessed for eligibility, four studies were excluded due to their lack of direct correlation between iron deficiency and HbA1c. Ultimately, this process included seven studies, ensuring that our review was based on the most relevant and high-quality research available.[17,21–26] PRISMA flow-diagram of the search process is shown in Figure 1.

Study and Population Characteristics

The seven studies obtained after the literature search and filtering included 365 participants, of which 283 were pregnant and 82 were non-pregnant. As shown in Table 1, the studies showcased a global interest in the relationship between IDA and HbA1c levels in pregnant and non-pregnant women, with research spanning Asia (Japan, Pakistan, India),[17,22–24] Africa (Sudan, Egypt),[21,26] and Europe (Turkey).[25] The most prevalent research design was cross-sectional studies,[21,22,26] complemented by a prospective cohort study,[22] two case-control studies,[23,24] and two quasi-experimental studies.[17,25] One of the included studies had divided their study into two parts, the first part included 47 patients and the second part involved 17 patients who were followed prospectively. Consequently, the analysis was conducted separately for each part.[22] The included studies collectively involved a wide range of sample sizes, from as few as 17 cases in Hashimoto et al (2008 [Part 2]) to as many as 47 cases in Hashimoto et al,[22] with a notable instance of a balanced case-control study by Hashimoto et al featuring 42 cases and 42 controls.[23]

The demographic profile of the participants varied, with the youngest mean age reported at 24.77 ± 4.07 years in Rafat et al and the oldest in the control group of Hashimoto et al at 31.6 ± 4.0 years.[17,23] Furthermore, the reported gestational ages indicated broad coverage of different pregnancy stages, from early (16 weeks gestational age) to late gestation (40 weeks gestational age).

Bias Assessment

The evaluation of bias across the included studies and their methodological approaches is summarised in Supplementary Table 4. Notably, the confounding domain had the lowest overall risk in the seven included studies. The studies done by Fadlelseed et al and Hashimoto et al (2008 [Part 2]) consistently showed low risk across all domains,[22,26] while the area of confounding presented a varied risk profile. There were intermediate risk levels in information and selection bias seen in studies such as Abdel-Aziz et al and Atzaz et al[21,24] The study by Atzaz et al was notable for its high risk of confounding variables affecting the control group.[24]

Iron Profiles in Pregnant versus Non-Pregnant Women

Iron profiles were reported in six of the seven included studies, as shown in Table 2. The studies reported different parameters indicating IDA (eg haemoglobin, ferritin, transferrin saturation, MCV). Two studies compared these parameters in pregnant and non-pregnant women.[23,24] The mean haemoglobin, ferritin, and transferrin saturation levels in pregnant women were 10.1 ± 1.44 g/dl, 9.78 ± 10.52 ng/mL, and 13.16 ± 7.91%, respectively. Conversely, non-pregnant women reported mean haemoglobin, ferritin, and transferrin saturation levels of 12.6 ± 2.12, 35.6 ± 44.13, and 26.2 ± 12.96, respectively. These findings indicate that pregnant women experience lower haemoglobin, ferritin, and transferrin saturation levels due to IDA within this particular group.

HbA1c in Pregnant versus Non-Pregnant Women

The HbA1c levels in pregnant women with IDA versus non-pregnant women are summarised in Table 3. Two studies comparing HbA1c levels in pregnant and non-pregnant women showed that pregnant women have a mean HbA1c of 5.85
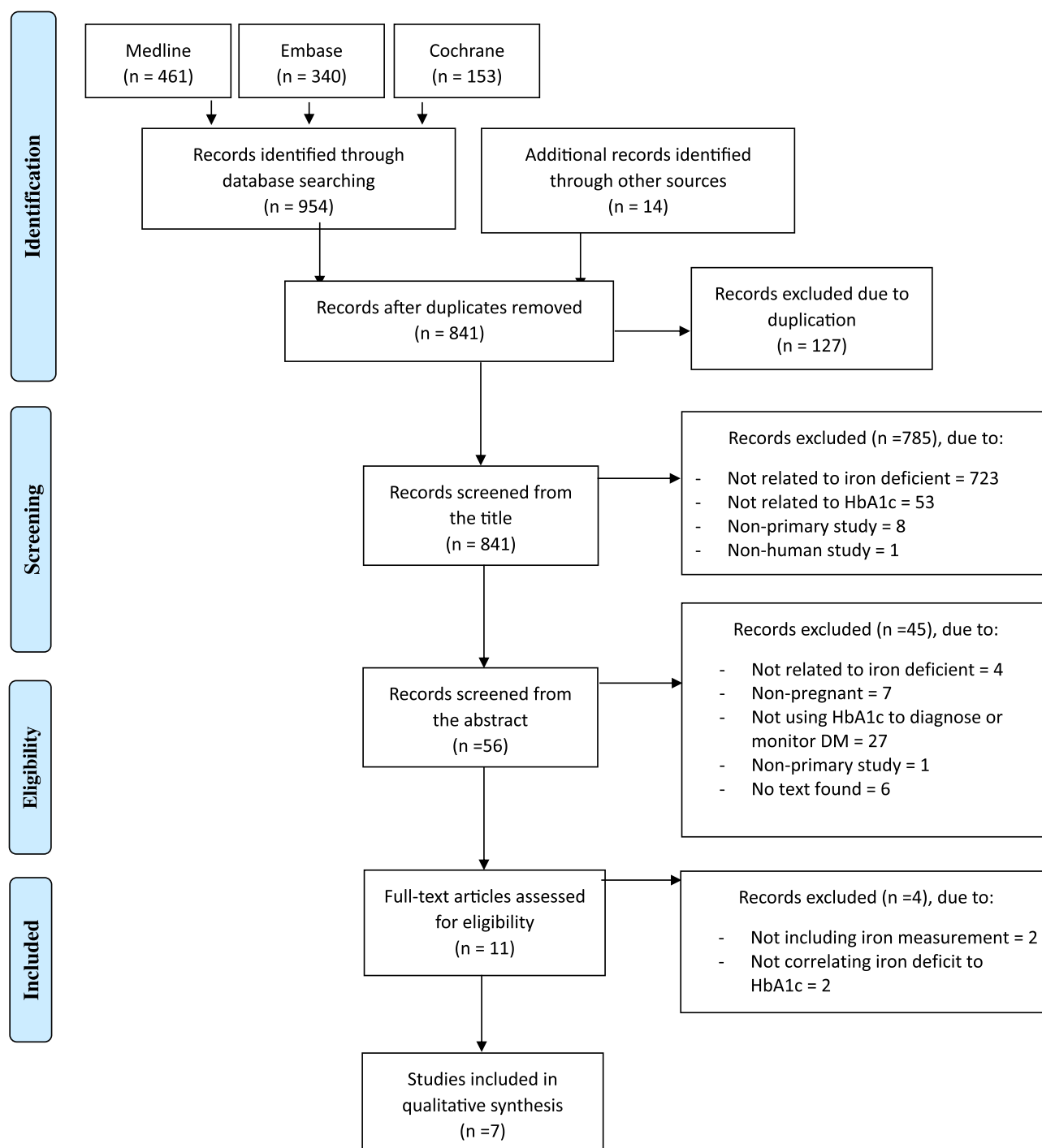
Figure 1 PRISMA flow-diagram of the search process.

± 3.24%, whereas non-pregnant women have a mean HbA1c of 4.62 ± 2.05%.[23,24] The mean level was higher in pregnant women, underscoring the impact of IDA on elevating glycaemic parameters in pregnancy.

The Overall Effect of IDA on HbA1c in Pregnant Women

Table 3 summarises the differences in HbA1c among the included studies. The aggregated data across the studies indicated an average HbA1c level of approximately 5.64 ± 0.97%. Among the individual studies, Atzaz et al reported the highest mean HbA1c in their cases at 6.81 ± 2.91%, which was significantly higher than the control's

Table 1 Baseline Characteristics of Included Articles

#	Author	Country	Sample size (Pregnant; Non-Pregnant)	Aim	Selection criteria		IDA Definition	GDM Definition	Gestational Age in Weeks
					Inclusion Criteria	Exclusion Criteria			
Cross-sectional study									
1	Fadlelseed, et al (2019)[26]	Sudan	(38; 0)	To evaluate the relationship between serum ferritin levels, IDA, and HbA1c levels in non-diabetic pregnant women.	Pregnant women with a single fetus.	Hypertension, GDM, chronic alcohol ingestion, renal diseases, and history of hemolytic anemia.	Hemoglobin less than 11 g/dL and serum ferritin level <15 µg/L.	FBG ≥92 mg/dL or 1-hour blood glucose was ≥180 mg/dL and/or 2-hour blood glucose ≥153 mg/dL, after 75-g oral glucose load.	26.8 ± 1.0
2	Abdel-Aziz, et al (2017)[21]	Egypt	(30; 0)	To investigate the association between serum levels of HbA1c with IDA in pregnant women.	Women between the ages of 20–40, with gestational age ranging from 20–40 weeks, who have uncomplicated pregnancies with a single fetus.	Multiple pregnancy, GDM, hypertension, chronic heart disease or bleeding conditions, women on iron therapy.	Hemoglobin less than 10 g/dL.	-	20–40
3	Hashimoto, et al (2008)[22]	Japan	(47; 0)	To evaluate the relationship between HbA1c and IDA in non-diabetic pregnant women.	Non-diabetic pregnant women with a gestational age between 21–36.	Receiving iron and vitamin supplementations during pregnancy.	-	Ambulatory plasma glucose levels <100 mg/dl.	28.5 ± 5.48
Prospective cohort study									
3	Hashimoto et al (2008) [Part 2][22]	Japan	(17; 0)	To evaluate the relationship between HbA1c and IDA in non-diabetic pregnant women.	Non-diabetic pregnant women with a gestational age between 21–36.	Receiving iron and vitamin supplementations during pregnancy.	-	Plasma glucose levels <100 mg/dl.	G1= 20–23 G2= 32–33
Case-control study									
4	Hashimoto, et al (2018)[23]	Japan	(42; 42)	To assess the relationship of IDA and HbA1c in pregnant and non-pregnant women.	Pregnant and non-pregnant women	Hepatic or renal diseases and/or subjects with high C reactive protein levels	Ferritin level <15 µg/L.	Plasma glucose levels <100 mg/dl.	27.5 ± 5.1

5	Atzaz, et al (2017)[24]	Pakistan	(42; 40)	To investigate the relationship between IDA in pregnant women and HbA1c.	Women between the ages of 20–40, with gestational age ranging from 20–40 weeks, who have uncomplicated pregnancies with a single fetus.	Multiple pregnancy, GDM, hypertension, chronic heart disease or bleeding conditions, women on iron therapy.	Hemoglobin less than 11 g/dL, serum ferritin < 12 μg/L, serum iron <10 mmol/L, TIBC >81 mmol/L and transferrin saturation <10%.	HbA1c < 6.5%.	20–40
Quasi-experimental study									
6	Eser, et al (2018)[25]	Turkey	(37; 0)	To examine the changes in HbA1c levels in pregnant women with IDA after their anemia has been treated.	Pregnant women with IDA.	Hemoglobinopathy, GDM, or Type I–II diabetes mellitus.	Hemoglobin level <11 g/dL in the first and third trimesters or <10.5 g/dL in the second trimester.	Fasting plasma glucose levels >110 mg/dL and 50-gram glucose challenge test >140 mg/dL.	25.0 ± 2.5
7	Rafat, et al (2012)[17]	India	(30; 0)	To investigate the correlation between HbA1c and erythrocyte indices in pregnant women without diabetes. Additionally, it seeks to evaluate the impact of iron supplementation on HbA1c levels.	Non-diabetic pregnant women.	Blood, transfusion, acute blood loss, hemolytic anemia, GDM, or BMI >25.	-	-	-

Abbreviations: IDA, iron deficiency anemia; GDM, gestational diabetes mellitus; HbA1C, hemoglobin A1c.

Table 2 Baseline Characteristics of IDA Parameters in Pregnant and Non-Pregnant Ladies

#	Author	Haemoglobin in g/dl		Ferritin in ng/mL		Transferrin Saturation in %		Iron Level in mmol/L		MCV in fL		MCH in pg	
		Pregnant	Non-Pregnant	Pregnant	Non-Pregnant	Pregnant	Non-Pregnant	Pregnant	Non-Pregnant	Pregnant	Non-Pregnant	Pregnant	Non-Pregnant
Cross-sectional study													
1	Fadlelseed, et al (2019)[26]	10.9 ± 0.7	-	20.7 ± 6.4	-	-	-	-	-	-	-	-	-
2	Abdel-Aziz, et al (2017)[21]	-	-	-	-	-	-	-	-	-	-	-	-
3	Hashimoto, et al (2008)[22]	-	-	-	-	-	-	-	-	-	-	-	-
Prospective cohort study													
3	Hashimoto et al (2008) [Part 2][22]	G1= 11.0 ± 0.5** G2= 10.6 ± 0.9***	-	G1= 17.4 ± 14.3** G2= 28.8 ± 2.4***	-	G1= 21.7 ± 10.4** G2= 12.5 ± 7.9***	-	-	-	-	-	G1= 30.2 ± 1.5** G2= 28.8 ± 2.4***	-
Case-control study													
4	Hashimoto, et al (2018)[23]	10.8 ± 0.7	12.6 ± 1.3	11.4 ± 11.1	29.6 ± 26.0	18.4 ± 11.8	31.2 ± 19.0	-	-	-	-	30.0 ± 2.1	29.4 ± 2.7
5	Atzaz et al (2017)[24]	9.39 ± 2.18	12.6 ± 2.93	8.15 ± 9.93	41.6 ± 18.13	7.91 ± 4.01	21.2 ± 6.91	7.2 ± 1.98	20.21 ± 6.81	-	-	-	-
Quasi-experimental study													
6	Eser, et al (2018)[25]	9.8 ± 0.9	-	6.3 ± 2.1	-	-	-	-	-	71.2 ± 8.1	-	22.7 ± 3.4	-
7	Rafat, et al (2012)[17]	7.1 ± 1.3	-	8.1 ± 1.4	-	-	-	22.1 ± 4.7	-	80.8 ± 7.8	-	25.5 ± 3	-

Notes: **G1: gestational age between 20–23; ***G2: gestational age between 32–33.

Table 3 HbA1c Level in Pregnant and Non-Pregnant Women

#	Author	IDA patients (n)	IRT supplemented patients (n)	HbA1c measurement method	HbA1c (%)		HbA1c (Post-IRT) (%)			The effect of IDA on HbA1c	The effect of IRT on HbA1c
					Pregnant	Non-pregnant	HbA1c %	Dose	Follow up period		
Cross-sectional study											
1	Fadlelseed, et al (2019)[26]	38	-	Roche Tina-quant HbA1c assay	4.4 ± 0.4	-	-	-	-	No change*	-
2	Abdel-Aziz, et al (2017)[21]	30	-	HPLC	6.33 ± 0.92	-	-	-	-	Increase*	-
3	Hashimoto, et al (2008)[22]	47	-	Latex aggregation immunoassay	4.4 ± 0.1	-	-	-	-	Increase*	-
Prospective cohort study											
3	Hashimotoet al (2008) [Part 2][22]	17	-	Latex aggregation immunoassay	G1= 4.4 ± 0.2** G2= 4.8 ± 0.2***	-	-	-	-	Increase*	-
Case-control study											
4	Hashimoto, et al (2018)[23]	42	-	HPLC	4.88 ± 0.33	5.14 ± 0.22	-	-	-	Increase*	-
5	Atzaz, et al (2017)[24]	42	-	-	6.81 ± 2.91	4.10 ± 1.83	-	-	-	Increase*	-
Quasi-experimental study											
6	Eser, et al (2018)[25]	37	37	Direct enzymatic HbA1c assay	5.01 ± 0.39	-	4.69 ± 0.38	Not reported	1 month	Increase	Decrease*
7	Rafat, et al (2012)[17]	30	30	HPLC	5.19 ± 0.32	-	5.1 ± 0.3	Not reported	3 months	Increase*	Decrease*

Notes: * P value <0.05 (statistically significant); **G1: gestational age between 20–23; ***G2: gestational age between 32–33.
Abbreviation: HPLC, High-performance Liquid Chromatography.

mean, pointing to the impact of IDA on elevating their cases' glycaemic parameters.[24] In contrast, Hashimoto et al presented a lower HbA1c mean of 4.88 ± 0.33% in cases compared to non-pregnant women having a mean HbA1c of 5.14 ± 0.22%, suggesting that the elevation of HbA1c secondary to IDA is more pronounced in non-pregnant women.[23]

This variation indicates the extent to which IDA can influence glycaemic parameters, potentially due to varying gestational ages and HbA1c measurement techniques. The most common HbA1c measurement technique was high-performance liquid chromatography (HPLC), which was used in three studies.[17,21,23] Other techniques included the Roche Tina-quant HbA1c assay, latex aggregation immunoassay, and direct enzymatic HbA1c assay. In addition, six of the included studies found a positive correlation between IDA and HbA1c levels, as lower haemoglobin levels were related to higher HbA1c levels.[17,21–25] In contrast, Fadlelseed et al showed that HbA1c levels were unrelated to IDA.[26] These individual study results, along with the computed averages and standard deviations, provide a comprehensive picture of IDA's variability and potential effects on HbA1c levels in pregnant women. The overall analysis underscores the significant association between IDA and elevated HbA1c levels.

The Overall Effect of IRT on HbA1c in Pregnant Women

Table 3 also discusses the effect of IDA on HbA1c before and after IRT in pregnant women, as represented in two studies.[17,25] They reported that HbA1c in pregnant women with IDA could change from an average of 5.1 ± 0.36% to 4.89 ± 0.34% after IRT. Although the duration of IRT ranged from one to three months, the dose and route of IRT were not mentioned in these studies. These results showed a significant decrease in HbA1c after IRT, highlighting the potential for reversing IDA's impact on glycaemic parameters with an appropriate IRT regimen.

Discussion

Many relationship between IDA and HbA1c is a subject of research, with several studies suggesting that IDA is associated with higher HbA1c levels in diabetic and nondiabetic males and non-pregnant women,[31–40] while others propose a contrary association.[41–45] The literature contains different systematic reviews and meta-analyses that discuss the correlation between IDA and HbA1c levels in this group.[46–50] However, a few studies have discussed their correlation in pregnant women with IDA.[17,21–26] This study conducted a comprehensive review of published data on the effect of IDA on HbA1c among pregnant versus non-pregnant women. This study found that the average HbA1c level was higher among pregnant women in comparison to non-pregnant women. Additionally, the mean HbA1c level in pregnant women decreased after the use of IRT.

Seven studies were included in this review. Six studies showed a significant positive correlation between HbA1c and IDA, where pregnant women with IDA exhibited higher levels of HbA1c.[17,21–25] These findings are consistent with the hypothesis that IDA can lead to falsely elevated HbA1c levels. Conversely, the remaining study showed divergence, indicating no effect of IDA on HbA1c.[26] This could be attributed to the idea that the study used a different method to measure HbA1c (Roche Tina-quant HbA1c assay), while the most common technique used in the other studies was HPLC. Although HPLC is widely recognised as the benchmark technique for analysing HbA1c levels, its implementation can be challenging for many laboratories due to its high cost, time-intensive nature, and the need for specialised technical expertise. These factors make it difficult for every laboratory to adopt HPLC as a routine method for HbA1c analysis.[51]

HbA1c levels can differ between pregnant and non-pregnant women. We found that HbA1c levels were slightly elevated in pregnant women with IDA compared to non-pregnant women. This increase is primarily attributed to hormonal fluctuations, heightened insulin resistance, and the need for nutrients to support foetal development, contributing to elevated blood glucose levels, which consequently leads to higher HbA1c levels.[52] Moreover, IDA can disrupt glucose metabolism and insulin sensitivity; hence, individuals with IDA may experience higher blood glucose levels, which can be reflected in elevated HbA1c readings.[53,54]

These findings underscore the need for caution when interpreting HbA1c levels in pregnant women. The elevated levels of HbA1c during pregnancy can result in significant maternal complications (eg GDM, preeclampsia, increased likelihood of caesarean delivery) and foetal complications (eg macrosomia, neonatal hypoglycaemia, and an increased susceptibility to birth defects).[55,56] However, incorrect interpretations of HbA1c levels can result in the misdiagnosis of

GDM in the presence of IDA. Therefore, this can lead to the belief that GDM is present and prompt the implementation of unnecessary treatment measures in pregnancy, which highlights the importance of comprehending the potential impact of IDA on HbA1c.

IRT has been shown to have a possible impact on decreasing HbA1c levels. Studies have reported a decrease in HbA1c after undergoing IRT, suggesting that it can effectively reduce HbA1c levels.[46] Similarly, this study found that there was a significant decrease in HbA1c after receiving IRT in pregnant women with IDA. These findings could be attributed to the fact that iron plays a critical role in creating haemoglobin. By replenishing iron levels, the production of haemoglobin improves, leading to a proportional increase in haemoglobin and a decrease in relative glycation (ie HbA1c levels).

Although this study is the first to provide a comprehensive review of the effects of IDA and IRT on HbA1c in pregnant women, we acknowledge some limitations. First, observational studies can have unmeasured confounders. Second, the studies included in this systematic review demonstrated substantial heterogeneity in various aspects, including sample size, study design, recruitment methods, HbA1c measurement techniques, and IRT follow-up duration. Third, our study was constrained by the overrepresentation of pregnant women and the relatively small sample sizes of the included studies. Fourth, including only two studies involving non-pregnant women and two studies examining the use of IRT poses limitations on the feasibility of conducting a meta-analysis. As a result, the findings should be regarded as preliminary and cannot be generalised to any specific population. Finally, it is essential to acknowledge the restricted quantity and breadth of the studies reviewed, which could potentially introduce bias into the systematic review findings due to publication and reporting biases.

Conclusion

This systematic review highlights an important topic with implications for pregnant women with IDA: they tend to have higher HbA1c levels compared to non-pregnant women. In addition, the use of IRT has shown preliminary findings in reducing HbA1c levels in pregnant women with IDA. Therefore, this study emphases on the need for IDA screening in pregnant women before interpreting HbA1c levels, considering a broader range of diagnostic indicators rather than relying solely on HbA1c levels, and treating IDA before determining the necessity of initiating antidiabetic medication in this group of individuals. However, it is essential to note that the findings of this study are inconclusive due to the limited number of studies reviewed. Hence, there is a critical need for further large-scale studies to better understand the relationships between IDA, IRT, and HbA1c during pregnancy.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising, or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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